Sex differences in Lemierre syndrome: Individual patient-level analysis

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Lemierre syndrome (LS) is a rare, but potentially fatal complication of an acute bacterial infection of the head-neck district, characterized by local thrombophlebitis and peripheral septic embolization, mainly affecting otherwise healthy adolescents and young adults, and typically associated with the Gram-negative rod *Fusobacterium necrophorum*. Despite modern antibiotic therapy, 4% of the patients died and 10% had disabling long-term sequelae in cases described after 2000 [1]. Little is known of the epidemiology and clinical course of LS, and sex differences have never been investigated so far. Yet, the pathophysiology of LS may involve an interplay of the coagulation cascade with components of innate and adaptive immunity [2] known to display sex differences [3], particularly in bacterial sepsis [4] and in the age groups most affected by LS [5]. Since the condition has a prominent thrombotic component, the known sex differences in non-septic venous thromboembolism may also apply to it.

In this retrospective analysis, we analysed sex differences in presentation, clinical course and impact of prognostic factors in 712 patients with LS. As previously described [1,6], all cases of patients with LS were retrieved that were reported globally between 2000 and 2017, without restriction of language or study design, in Medline, Embase, the Cochrane Library, the grey literature and the references of retrieved articles, and the publishing authors were contacted individually to integrate the search. The criteria for LS were: (i) primary head/neck bacterial infection; (ii) objectively confirmed head/neck thrombosis or peripheral (embolic) septic lesion. Among the cases meeting this broad definition of LS, we distinguished those with *typical* LS, which is restricted to cases with oropharyngeal infection and proved isolation of *Fusobacterium* spp. [7]. In all cases, we noted sex, age, typical vs. atypical LS, previous medical contacts before diagnosis, bacterial isolation, and location of thrombosis and septic lesions at presentation. In cases providing data on the clinical course beyond presentation, we recorded treatment and clinical outcomes, which included objectively diagnosed (i) new/recurrent venous thromboembolism, (ii) new/worsening peripheral (embolic) septic lesions, (iii) major bleeding, and (iv) death from all causes, either in-hospital or within 30 days from diagnosis; and, in survivors, clinical sequelae present at discharge, which included neurological complications or other functional limitations.

Sex distribution was assessed using the binomial test for the deviation from a 1:1 ratio. Clinical features at presentation and treatment patterns were analysed descriptively, with categorical variables shown as frequency (percentage), non-normally distributed continuous variables as median (interquartile range). Sex differences in clinical outcomes were compared using the chi-square test; sex differences in the association between clinical characteristics of interest and early complications (new/recurrent venous thromboembolism or new peripheral septic lesion after diagnosis) were studied using the odds ratios (ORs) with 95% CI estimated by multivariable logistic regression in a model run for females and males separately, with interaction with sex tested by adding the interaction terms of each explanatory variable with sex to a single model run on the whole sample.

A total of 712 patients had information on clinical presentation and diagnosis and were used for the analysis of sex distribution and sex differences in clinical presentation, while 652 patients, for whom hospital follow-up data up to discharge or beyond was available, were used for the analysis of sex differences in the clinical course and in the association between variables of interest and early complications.

Of the 712 patients, 295 (41.4%, 95% CI 37.8%–45.2%) were female and 417 (58.6%, 95% CI 54.8%–62.2%) male. Clinical features at presentation were similar in female and male patients, with females marginally younger than males (median: 20, IQR: 16–32 years; vs. median: 22, IQR: 18–34 years). The most common primary infections were oropharyngeal (214/295 of female patients and 306/417 of male patients), and the most commonly isolated bacterial genus *Fusobacterium* (55.6% of females and 60.2% of males). A total of 235 (79.7%) female and 347 (83.2%) male patients had concomitant peripheral (embolic) septic lesions, most often pulmonary in both sexes (206, 69.8%; and 300, 71.9%, respectively). Typical LS was diagnosed in 129 (43.7%) of female and 204 (48.9%) of male patients (Table 1).

In the 652 patients with in-hospital follow-up, we observed no evident differences in treatment patterns between sexes. Antibiotics were used in almost all patients (98.5% of female and 99.5% of male patients) and anticoagulation in 146/272 (53.7%) female and 216/380

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(56.8%) male patients. Surgical procedures were carried out in 133/272 (48.9%) female and 204/380 (53.7%) male patients.

Clinical outcomes were also similar across sexes. Early complications, including new/recurrent venous thromboembolism or new/worsening peripheral septic lesions, were observed in 40/272 (14.7%) female and 53/380 (13.9%) male patients, major bleedings in 6/272 (2.2%) female and 13/380 (3.4%) male patients. A total of 12/272 (4.4%) female and 14/380 (3.7%) male patients died. Sequelae at discharge were described in 32/260 (12.3%) female and 33/380 (9.0%) male survivors (Table 1).

Multivariable logistic regression with interaction analysis showed that in female patients, but not in male patients, positive cultures for *Fusobacterium* spp. were independently associated with early complications (in female patients: OR 3.06, 95% CI 1.33 to 7.75; in male patients: OR 0.88, 95% CI 0.46, 1.73; p value for the interaction sex-isolation of *Fusobacterium* spp.: 0.034; Table 2). No other sex differences were found in the association between clinical characteristics at baseline and risk of early in-hospital complications, with intracranial involvement at baseline retaining a strong independent association with in-hospital complications in both sexes (OR 3.00, 95% CI 1.42 to 6.37 in female patients; OR 2.06, 95% CI 1.06 to 3.91 in female patients; p value for the interaction: 0.430).

Table 1
Presentation and clinical course of 712 patients with Lemierre syndrome.

Presentation and diagnosis	Total (N = 712)	Female (N = 295)	Male (N = 417)
Age (years), median (IQR)	21 (17–33)	20 (16–32)	22 (18–34)
Typical Lemierre syndrome, n (%)	333 (46.8)	129 (43.7)	204 (48.9)
Previous medical contacts before diagnosis, n (%)	286 (40.2)	115 (39.0)	171 (41.0)
Primary head and neck infection			
Oropharyngeal, n (%)	520 (73.0)	214 (72.5)	306 (73.4)
Low respiratory tract, n (%)	330 (46.3)	130 (44.1)	200 (48.0)
Neck, n (%)	287 (40.3)	117 (39.7)	170 (40.8)
Other, n (%)	165 (23.2)	67 (22.7)	98 (23.5)
Bacteria isolated (any), n (%)	583 (81.9)	236 (80.0)	347 (83.2)
Gram-positive, n (%)	180 (25.3)	71 (24.1)	109 (26.1)
Gram-negative, n (%)	474 (66.6)	192 (65.1)	282 (67.6)
Fusobacterium spp., n (%)	415 (58.3)	164 (55.6)	251 (60.2)
Initial head/neck vein thrombosis, n (%)	597 (83.8)	247 (83.7)	350 (83.9)
Internal jugular vein thrombosis, n (%)	526 (73.9)	215 (72.9)	311 (74.6)
Cerebral vein thrombosis, n (%)	143 (20.1)	69 (23.4)	75 (18.0)
External jugular vein thrombosis, n (%)	43 (6.0)	18 (6.1)	25 (6.0)
Other, n (%)	116 (16.3)	48 (16.3)	68 (16.3)
Peripheral septic lesions, n (%)	582 (81.7)	235 (79.7)	347 (83.2)
Pulmonary, n (%)	506 (71.1)	206 (69.8)	300 (71.9)
Muscolo-skeletal, n (%)	108 (15.2)	37 (12.5)	71 (17.0)
Intracranial, n (%)	79 (11.1)	34 (11.5)	45 (10.8)
Other, n (%)	59 (8.3)	19 (6.4)	40 (9.6)

Clinical course and outcomes	Total (N = 652)	Female (N = 272)	Male (N = 380)
Antibiotic therapy, n (%)	646 (99.7)	268 (98.5)	378 (99.5)
Penicillins	357 (54.8)	154 (56.6)	203 (53.4)
Metronidazole	311 (47.7)	124 (45.6)	187 (49.2)
Cephalosporins	275 (42.2)	119 (43.8)	156 (41.1)
Other	434 (66.6)	171 (62.9)	263 (69.2)
Use of anticoagulation, n (%)	362 (55.5)	146 (53.7)	216 (56.8)
Low-molecular-weight heparin	229 (35.1)	89 (32.7)	140 (36.8)
Fondaparinux	6 (0.9)	1 (0.4)	5 (1.3)
Unfractionated heparin	76 (11.7)	33 (12.1)	43 (11.3)
Direct oral anticoagulants	3 (0.5)	2 (0.7)	1 (0.3)
Vitamin K antagonists, n (%)	131 (20.1)	56 (20.6)	75 (19.7)
Length of anticoagulation (days), median (IQR)	84 (21–120)	90 (28–95)	45 (21–90)
Surgical procedures, n (%)	337 (51.7)	133 (48.9)	204 (53.7)
Abscess drainage	245 (37.6)	87 (32.0)	158 (41.6)
Mastoidectomy	40 (6.1)	22 (8.1)	18 (4.7)
Jugular vein ligation or embolectomy	31 (4.8)	15 (5.5)	16 (4.2)
Other	114 (17.5)	44 (16.2)	70 (18.4)
Clinical outcomes			
New/recurrent venous thromboembolism, n (%)	34 (5.2%)	13 (4.8%)	21 (5.5%)*
New peripheral septic lesion, n (%)	76 (11.7%)	35 (12.9%)	41 (10.5%)*
Major bleedings, n (%)	19 (2.9%)	6 (2.2%)	13 (3.4%)*
Death, n (%)	26 (4.0%)	12 (4.4%)	14 (3.7%)*

Survivors	Total (N = 626)	Female (N = 260)	Male (N = 366)
Clinical sequelae, n (%)	65 (10.0%)	32 (12.3%)	33 (9.0%)*

Typical Lemierre syndrome consisted of acute oropharyngeal infection, isolation of *Fusobacterium* spp., and either head/neck vein thrombosis or peripheral (embolic) septic lesions. New/recurrent venous thromboembolism, new peripheral (embolic) septic lesion, major bleedings, and death were considered as Lemierre syndrome complications if they occurred after diagnosis and during hospitalization or within 30 days from the day of admission. IQR = Interquartile range.

* p value >0.05 upon chi-square test.

Table 2
Multivariable logistic regression analysis of the association between clinical characteristics and early complications, stratified by sex.

	Females, OR (95% CI)	Males, OR (95% CI)	*p* value for sex interaction[a]
Outcome events/patients	40/272	53/380	
Use of anticoagulation	0.55 (0.26–1.14)	0.60 (0.32–1.11)	0.81
Age (+1 year)	1.01 (0.98–1.03)	1.00 (0.98–1.02)	0.73
Intracranial involvement at baseline	3.00 (1.42–6.37)	2.06 (1.06–3.91)	0.43
Peripheral septic lesion at baseline	0.74 (0.30–1.94)	1.65 (0.68–4.67)	0.25
Isolation of *Fusobacterium* spp.	3.06 (1.33–7.75)	0.88 (0.46–1.73)	0.03
Use of anti-Fusobacterium antibiotics	1.19 (0.56–2.47)	1.44 (0.78–2.65)	0.68

Early complications were new/recurrent venous thromboembolism or new peripheral (embolic) septic lesions objectively diagnosed after the diagnosis of Lemierre syndrome and in-hospital or within 30 days from admission. Intracranial involvement at diagnosis was defined as cerebral venous thrombosis or intracranial suppuration at diagnosis. Peripheral (embolic) septic lesion at diagnosis was defined as any septic distance suppuration at diagnosis. The use of anticoagulants and of a combination of antibiotic therapy specific for *Fusobacterium* spp. was defined at the time of complication (cases) vs. during hospitalization (controls). OR = odds ratio. CI = confidence interval.

[a] Tested in a model run on the whole sample and including both main effects and interaction terms with sex for all covariates.

Our results suggest a male predominance in LS less marked than the ratio of 2:1 to 3:1 in favour of males repeatedly observed in septicaemia due to *Fusobacterium necrophorum*. This only slight male predominance held even when considering cases with *Fusobacterium* spp. isolation only or cases with typical LS only (data not shown). Rather, this finding is consistent with a recent nationwide study on exclusively *Fusobacterium*-associated LS which found a sex ratio of 1:1 [8], despite the fact that *Fusobacterium* spp. are not isolated in all cases of LS, and that other bacteria have been suggested to be responsible for the same clinical syndrome [7]. In this perspective, the slight male majority may reflect a moderate reporting bias favouring cases with *Fusobacterium* spp. isolation, in turn stemming from a detection bias – cases with *Fusobacterium* spp. isolation possibly being more often diagnosed as LS [9].

The overall clinical presentation of LS did not display obvious or potentially clinically relevant sex differences. In particular, the distribution of cerebral vein thrombosis did not match the known female preponderance of 3:1 in this condition [10], suggesting that its pathogenesis in LS follows a distinct pathway less strongly associated with sex.

The association of the isolation of *Fusobacterium* spp. with a worse in-hospital prognosis in female patients only is a novel finding that may reflect sex-specific differences in the immune reaction to *Fusobacterium*, with the possible implication of more aggressive monitoring or treatment required in case of a positive culture for *Fusobacterium* in female patients. Alternatively, this finding could reflect an intrinsic bias, with either *Fusobacterium* infections in female patients more likely to progress to an advanced stage than in males by the time medical attention is sought and a diagnosis reached (a form of detection bias) or, among advanced cases of LS with *Fusobacterium*, with this pathogen more likely to be isolated in female than male patients because it may have had more time to proliferate in the absence of appropriate or timely treatment (a form of performance bias). Lastly, selection bias could derive from the presence of cases of LS variants of urogenital origin among female patients who did not report urogenital infections or symptoms, but described a recent oropharyngeal infection – a common occurrence in the general population – and received a diagnosis of LS [7]. If these invasive infections have a worse prognosis than those from an oropharyngeal focus, this subpopulation would bias the association of *Fusobacterium* spp. with in-hospital complications among female patients in the way we observed. This possibility merits attention by specifically designed studies, as it would suggest that the finding of *Fusobacterium* spp. should prompt an accurate gynaecological history or examination, and calls for further standardization of the diagnostic criteria of LS.

Our analysis has a number of limitations. First, the associations observed do not imply causality and cannot support prediction. Second, we analysed cases reported by physicians and researchers; despite the inclusion of the grey literature and contact with the authors to include unpublished cases, reporting and publication bias cannot be excluded.

In conclusion, our study confirms a slight imbalance toward males of the distribution of LS, shows that no evident or potentially clinically relevant sex differences in the presentation or prognosis of LS support any sex-specific approach to its management, and suggests a worse in-hospital prognosis of female patients with an isolation of *Fusobacterium* spp. from biological specimens of potential clinical relevance.

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CRediT authorship contribution statement

LV: design of the study, statistical analysis, interpretation of the results, writing of the manuscript, final approval. FZ, CS, AP: study design, data collection, interpretation of the results, critical revision of the manuscript, final approval. GC, SG, KH, MH, MJ, TN, CR: data collection, interpretation of the results, critical revision of the manuscript, final approval. NK, CR, AT, SK: interpretation of the results, critical revision of the manuscript, final approval. SB: concept and design of the study, supervision, data collection, interpretation of the results, writing of the manuscript, final approval.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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